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# Erlotinib or Gefitinib for the Treatment of Relapsed Platinum Pretreated NSCLC and Ovarian Cancer: a Systematic Review

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**Abstract**

**Background:** Platinum-based chemotherapy is the standard of care for ovarian cancer and non-small cell lung cancer (NSCLC). However, resistance to platinum agents invariably develops. Targeted therapies, such as tyrosine kinase inhibitors (TKIs), have great potential here as they exert their anti-tumour effect *via* alternative mechanisms to platinum-based drugs and as such may remain unaffected by emergent resistance to platinum.

**Methods:** A systematic review was conducted to investigate whether two EGFR-TKIs, erlotinib and gefitinib, have efficacy in the platinum-resistance setting. Preclinical studies of platinum-resistant cancer cell lines, which had been subsequently treated with EGFR-TKIs, were sought to establish proof-of-concept. Clinical trials reporting administration of EGFR-TKIs to ovarian cancer and NSCLC patients relapsed after therapy with platinum drugs were investigated to determine sensitivity of these cohorts to EGFR-TKI treatment. The role of EGFR mutation, copy number and protein expression on response to EGFR-TKIs after failure of platinum chemotherapy were also investigated.

**Results:** Preclinical models of platinum-resistant cancer were found which display a spectrum of cross-resistance profiles to EGFR-TKIs. Sensitivity to EGFR-TKIs is dependent on the activation of the EGFR pathway or EGFR interacting proteins such as HER-2. EGFR-TKIs show favourable response rates in platinum-pretreated NSCLC, 11.14% and 15.25% for 150 mg/day erlotinib and 250 mg/day gefitinib, respectively. These response rates significantly improve in patients of Asian descent (28.3% and 29.17%, respectively) and patients with EGFR activation mutations (41.6% and 63.89%, respectively) or increased copy number (33.3% and 45.45%, respectively). Gefitinib significantly outperformed erlotinib and should therefore be the EGFR-TKI of choice in platinum-pretreated relapsed NSCLC. In contrast, response rates are very poor to both erlotinib and gefitinib in platinum pretreated ovarian cancer, 0-5.9% and they should not be used in this cohort of patients.

Preclinical models demonstrate that, while cross resistance can occur between platinums and EGFR-TKIs, there is not a generalised cross-resistance phenotype. Erlotinib and gefitinib are suitable for the treatment of platinum-pretreated NSCLC, particularly in patients with EGFR mutations or increases in copy number. Unfortunately, the high rates of EGFR protein overexpression in ovarian cancer are not translating to a clinically useful therapeutic target for EGFR-TKIs; EGFR mutations are rare in ovarian cancer. Newer TKIs may improve response rates in these cohorts and future clinical trials need to collect tumour biopsies from all patients to ensure the success of personalised chemotherapy.

## 1. Introduction

The lungs are the most common site of cancer occurrence when both genders are considered together (12.7% of cancer cases); lung cancer also results in the greatest mortality by site of cancer origin (18.2%) (Ferlay et al., 2008). Amongst lung cancer subtypes, those characterised as non-small cell lung cancers (NSCLCs) are the most prevalent (89%) and prognosis is poor for advanced stages of the disease – 5 year survival is estimated to be 10% for stage IIIA and 4% for stage IV (Yang et al., 2005). Similarly, for ovarian cancer, estimated to be the seventh most common cause of mortality in women due to invasive cancers worldwide (Ferlay et al., 2008), survival worsens with disease progression – 5 year survival among a US population up to 2001 was estimated to be 33.5% and 17.9% for stages III and IV ovarian cancer, respectively, compared with 53.8% survival after 5 years across all stages (Ries et al., 2007). At an advanced stage, these cancers have developed lymph node metastases or have proliferated across the peritoneum in the case of many ovarian cancers. This distribution limits surgical options and hence chemotherapy is the standard of care. Typically, this comprises a platinum/taxol drug combination regimen (Vasey et al., 2005; Rajeswaran et al., 2008). While a moderate percentage of patients initially respond well after first-line chemotherapy, recurrence of disease is commonly observed, with only modest response rates in a substantial number of such cases. Recurrence is frequently accompanied by resistance to the platinum-based chemotherapy administered as first-line treatment. In the case of ovarian cancer, drug resistance is demarcated by a re-emergence of detectable disease within 6 months of documented regression following platinum treatment (Markman et al., 1992). The resistance to chemotherapy highlights the necessity for anti-cancer agents which operate *via* different mechanisms than that of platinum-based drugs.

Platinum-based anticancer drugs such as cisplatin and carboplatin cause cytotoxicity mainly due to interaction with DNA, forming inter- and intra-strand adducts, hindering RNA transcription and DNA replication, leading to cell cycle arrest and apoptosis. Inevitably, the use of platinum chemotherapy is limited by the development of drug resistance. Numerous cellular mechanisms potentially contributing to clinical platinum resistance have been proposed, including changes in cellular drug accumulation, detoxification of the drug, inhibition of apoptosis and DNA repair of platinum adducts (Stordal et al., 2007a; Shahzad et al., 2009; Brabec and Kasparkova, 2005; Borst et al., 2008).

Research and evaluation of chemotherapeutic treatment options for platinum-resistant cancer take several approaches: i) development of novel cytotoxic agents for first-line monotherapy; ii) addition of a third cytotoxic agent to standard first-line platinum/taxane doublet therapy and iii) addition of a molecularly-targeted agent to first-line or salvage therapy (Goffin et al., 2010; Triano et al., 2010). In the targeted-agent approach, receptor tyrosine kinases are currently mainstay as potential targets, because

they have a central role in development, survival and proliferation of cancer cells (Hynes et al., 2005) related to their frequent dysregulation and/or gain-of-function mutations, evident in NSCLC (Hirsch et al., 2003; Rusch et al., 1993) and ovarian cancer (Lafky et al., 2008). The pre-eminent tyrosine kinase targets are those of the epidermal growth factor receptor (EGFR) tyrosine kinase family, also known as ErbB (avian erythroblastosis oncogene B) or HER (human epidermal growth factor receptor), in particular EGFR (Erb1). After binding with their ligands, tyrosine kinase receptors trigger a cascade of phosphorylation and activation of signalling pathways which have the overall effect of increasing tumor cell proliferation, angiogenesis, invasion and metastasis as well as inhibiting apoptosis (Rosa et al., 2008). Each family member dimerises with another upon ligand binding, with HER2 being the preferred partner, this is necessary for HER2 activity as it lacks a cognate ligand. It is thought that HER2 mediates growth and survival of cancer cells by activation of the PI3K/AKT and MAPK signalling pathways, while their invasive potential may be modulated *via* NF-κB signalling (Merkhofer et al., 2010).

EGFR may possess one of several commonly observed mutations coinciding with aberrant activity of the receptor, including an altered response to EGFR tyrosine kinase inhibitors (TKIs) and, therefore, altered clinical efficacy. These are most often substitution mutations or in-frame deletions arising in exons 19 or 21 (City of Hope Molecular Diagnostic Laboratory, 2010). In NSCLC, mutations at these sites alter the tyrosine kinase domain and are associated with improved response rate to EGFR-TKI treatment *versus* tumours expressing wild type EGFR. These mutants may in fact be associated with a state of addiction of the tumour cell to their activity, therefore sensitising the cell to EGFR-TKIs and accounting for the observed clinical efficacy of erlotinib and gefitinib (Gazdar et al., 2004). Conversely, tumours expressing the exons 2–7 deletion mutant, EGFRvIII, which affects the extracellular domain of the protein, are relatively unresponsive to treatment by erlotinib or gefitinib (Ji et al., 2006). Resistance to EGFR-TKI treatment may also be acquired following selection of cells which have either developed a de-sensitising mutation or been present as a subset in the pre-treatment tumour, for example the T790M mutation, which occurs in up to 50% of NSCLC or lung adenocarcinoma (Balak et al., 2006; Kosaka et al., 2006; Sharma et al., 2007).

For unselected patient cohorts, the overall response to treatment with EGFR-TKIs is relatively low. However, retrospective analysis of NSCLC tumour samples reveals a high percentage of EGFR mutations in patients who had responded to the EGFR-TKI gefitinib as salvage chemotherapy, 88.8%, n=9 (Lynch et al., 2004). The rate of EGFR mutations in NSCLC is relatively high and varies by ethnicity, with tumours from patients of Asian extraction displaying substantially higher rates of occurrence; 15/58 (25.8%) mutations in Japanese patients compared with 1/61 in non-Asian patients from the USA (1.6%) (Paez et al., 2004). For many other commonly occurring solid tumours,

the incidence of mutations in EGFR is very low or non-existent. Lee *et al.* examined 536 tumours from colon, gastric, breast, hepatic cancers and adult leukaemias. Only one EGFR mutation was detected in a breast carcinoma, but it was a silent mutation not affecting the protein sequence (Lee et al., 2005a). EGFR mutations have not been detected in cervical cancer (Arias-Pulido et al., 2008). This is also the case for ovarian cancer, where often no deleterious EGFR mutations are detected in a group of patients (Lacroix et al., 2006; Lassus et al., 2006; Steffensen et al., 2008). However, high rates of EGFR mutations have been seen in Asian ovarian cancer patients, 23.5% (Takana et al., 2011).

However, there may be a role for EGFR-TKIs in tumours which do not have EGFR mutations, such as ovarian cancer, if there is an activation of the EGFR pathway either as part of the carcinogenesis of the tumour or as a response to first-line chemotherapy. Increased copy number of EGFR as determined by FISH occurs in 12-20% of ovarian carcinomas (Lassus et al., 2006; Stadlmann et al., 2006; Vermeij et al., 2008). EGFR protein overexpression occurs in 17-38% of ovarian tumours as determined by immunocytochemistry (Lassus et al., 2006; Stadlmann et al., 2006; Vermeij et al., 2008). Increased EGFR copy number and protein expression have also been associated with poor patient outcome in ovarian cancer (Lassus et al., 2006). Treatment with an EGFR-TKI may improve the prognosis of this cohort of ovarian cancer patients**.** This systematic review will examine the effect of EGFR mutation in NSCLC and EGFR activation in ovarian cancer on the response to treatment with EGFR-TKIs after failure of platinum-based chemotherapy.

The correlation between EGFR expression and response to EGFR-TKIs has been studied extensively. Ono and colleagues investigated the relationship between EGFR expression by western blot and response to gefitinib; they saw a correlation in their panel of NSCLC cell lines (Ono et al., 2004). In contrast, Suzuki and colleagues investigated the relationship between EGFR, pEGFR, HER-2 protein expression, and KRAS gene mutation and response to erlotinib in a panel of 19 NSCLC cell lines; they found no correlation of any of these markers, as determined by western blot and PCR, with the $IC_{50}$ of erlotinib (Suzuki et al., 2003). The lack of correlation between EGFR and pEGFR expression and the activity of EGFR-TKIs is discouraging; however these still remain the first biomarkers to investigate to predict the response to EGFR-TKIs. This systematic review will examine a range of biomarkers in preclinical studies in order to accurately categorise a cell line or cancer patient as potentially EGFR-TKI sensitive.

The development of cisplatin resistance in cell lines can also alter the expression of EGFR and pEGFR and activate the pathway. A panel of four cisplatin-resistant neuroblastoma cell lines have also been shown to have increased EGFR and pEGFR protein expression and be more sensitive to treatment with novel EGFR-targeted agents than their cisplatin-sensitive counterparts (Michaelis et al., 2008). Similar results were

seen in two cisplatin-resistant oral carcinoma cell lines, increased EGFR and pEGFR and sensitivity to the novel EGFR inhibitor AG1478 (Hiraishi et al., 2008). Therefore, treatment with platinum and the development of platinum resistance may cause EGFR dysfunction by altering the protein expression and activity of components of the EGFR pathway in a subpopulation of relapsed cancer patients. Therefore, we hypothesise that EGFR-TKIs could be useful in treating platinum pretreated and/or platinum-resistant cancers if a dysfunction in the EGFR pathway has developed as a result of first-line platinum-based chemotherapy. Identifying this subpopulation may yield better response rates to salvage chemotherapy with EGFR-TKIs.

Erlotinib and gefitinib are both EGFR-TKIs, which bind the ATP-binding site in the cytosolic EGFR tyrosine kinase-domain, preventing autophosphorylation and activation of key signalling pathways (Rosa et al., 2008, Yun et al., 2008). Both have been FDA-approved for the treatment of advanced or metastatic NSCLC where foregoing chemotherapy has failed and, therefore, are the focus of this review in the context of their suitability as targeted salvage treatment agents for NSCLC and ovarian cancers which have recurred after treatment with platinum-based chemotherapy.

## 2. Methods

### *2.1. Data collection*

Medline and EMBASE were searched systematically for preclinical and clinical studies reporting outcomes of platinum-resistant ovarian/non-small cell lung cancer cell lines and tumours treated with either erlotinib or gefitinib. The literature searches were performed by both review authors independently and last updated in February 2011. The searches were limited to papers published in the English language only. Conference abstracts and review articles were excluded from the analysis.

#### *2.1.1. Preclinical*

A keyword search strategy was utilised, combining relevant words or their common synonyms for:-

1) Cancer types (cancer*, carcinom*, neoplas*, tum*, malignan*, ovar*, NSCLC),

2) Platinum drugs (platin*, cisplatin, oxaliplatin, carboplatin, CDDP),

3) EGFR-TKIs (gefitinib, Iressa, ZD1839, erlotinib, Tarceva, OSI-774)

4) Drug resistance status (resist*, cross resist*, toxicity, $IC_{50}$).

5) Preclinical (cells or cell line).

Resistance studies looking at a panel of cancer cell lines and the relative resistance between them were excluded, as these studies examine intrinsic platinum resistance and not resistance developed from exposure to chemotherapy. Resistant cell lines resulting from transfection were excluded.

#### *2.1.2. Clinical*

Medline and EMBASE were searched for all clinical trials using erlotinib or gefitinib alone or in combination as treatment for patients who had previously received cisplatin or carboplatin-based chemotherapy.

1) Cancer types (cancer*, carcinom*, neoplas*, tum*, malignan*, ovar*, NSCLC),

2) Platinum drugs (platin*, cisplatin, oxaliplatin, carboplatin, CDDP),

3) EGFR-TKIs (gefitinib, Iressa, ZD1839, erlotinib, Tarceva, OSI-774)

4) Second Line Therapy/ Drug-resistant Disease (resist*, refractory, relaps*, retreat*, re-treat*, pretreat*, pre-treat*, progress*, persistant, salvage, second-line)

5) Clinical Trial (trial, phase, patient*, group*, random*, cohort, random).

All studies of "first-line" or chemotherapy-naïve patients were excluded. Second line studies were excluded if patients had received no prior platinum chemotherapy. Case studies reporting less than 5 patients were excluded. Reports of maintenance chemotherapy for non-relapsed/ non-progressed platinum pretreated patients were excluded. Reports apparently relevant by reading of abstracts were scrutinised and, where relevant information was provided, data were extracted and tabulated. Relevant reviews were also examined in order to identify further studies not returned by searching of the databases. The reference lists of included studies were also searched for relevant papers. Where insufficient data had been presented, attempts were made to contact authors for clarification.

*2.3. Statistics*

The Fisher's exact test, using two tails for p values as calculated by Graphpad Quickcalc was used to test for significant differences between the pooled response rates in the clinical data. P values of less than 0.05 were considered significant.

## 3. Results

*3.1. Preclinical Studies*

Cell line models of acquired drug resistance are developed in the laboratory by repeatedly exposing cancer cells in culture to chemotherapeutic agents. Methodologies for development vary between laboratories, some use the same dose of chemotherapy with minimal dose escalation (Stordal et al., 2006; Locke et al.,1999), and others gradually increase the dose of chemotherapy the cells are exposed to over a longer time period (Akiyama et al., 1985; Clynes et al., 1992). The surviving resistant cells are then compared to the parental sensitive cells using a cell viability assay such as the MTT, acid phosphatase or clonogenic assay. The sensitivity of these paired cell lines to any particular drug is usually determined by exposing them to a range of drug concentrations and then assessing cell viability. The $IC_{50}$ (drug concentration causing 50% growth inhibition) for these paired cell lines can be used to determine the increase in resistance known as fold resistance by the following equation:-

Fold Resistance = $IC_{50}$ of Resistant Cell Line / $IC_{50}$ of Parental Cell Line

The literature search for models of acquired drug resistance which report cross-resistance data for both a platinum chemotherapeutic and erlotinib or gefitinib identified 4 papers reporting 10 cell lines **(Table 1)**. The definition of cross-resistance between two chemotherapy drugs is a matter of debate in the literature. Some studies consider two drugs cross-resistant only if a similar level of resistance is observed. Studies which have developed cell lines from patients before and after chemotherapy have found that drug resistance in the clinic typically produces resistance of 2- to 3-fold) (Kawai et al., 2002;

Kuroda et al., 1991). For the purposes of this review we have defined cross-resistance between platinums and EGFR-TKIs as greater than or equal to 2-fold resistance to both drugs. This definition is therefore based on what would be clinically observed as cross-resistance.

Dai *et al.* sought to investigate the relative efficacy of erlotinib in several human cancer-derived cell lines and their drug-resistant sublines **(Table 1)** (Dai et al., 2005). This included a cisplatin-resistant ovarian cancer cell line derived from A2780 cells, A2780/CDDP, which exhibited a 15-fold resistance to cisplatin. Their results indicated no change in resistance to erlotinib in A2780/CDDP compared to the parental A2870 cells (0.93-fold) and a decrease in expression of EGFR by western blot. These findings indicate that erlotinib might still be a potentially useful therapy in cisplatin-resistant ovarian cancer. Dai *et al.* showed increased sensitivity to erlotinib in the cisplatin-resistant cervical cancer cell line, AE-ME180/CDDP; this sensitivity correlated with the over-expression of EGFR protein and 'activated' pEGFR proteins. In contrast, two other cisplatin-resistant models studied by Dai *et al.,* HT212/11/CDDP and HT180/1/CDDP, also had increased EGFR protein but no increase in activated pEGFR protein. These two cell lines showed no change in erlotinib resistance suggesting that erlotinib sensitivity may be dependent on the activation of the EGFR pathway. Overall, this study suggests that erlotinib treatment might still be beneficial in a platinum pretreated patient population as no cross-resistance to erlotinib was gained in association with cisplatin resistance.

Chin *et al.* investigated the efficacy of erlotinib in a NSCLC-derived cell line, PC9, harbouring an EGFR mutation (single exon 19 deletions ΔE746-A750). They also examined PC9(CR), a model with acquired resistance to cisplatin (Chin et al., 2008). In a short term cytotoxicity assay they found that cisplatin-resistance was associated with low level resistance to erlotinib **(Table 1).** Interestingly, in a longer term clonogenic assay, they found a 5-fold increase in resistance to erlotinib in the cisplatin-resistant PC9 cells which persisted even after discontinuation of cisplatin treatment. The cisplatin-resistant PC9(CR) cells had a decrease in EGFR protein expression and a slight increase in pEGFR. However, the mechanism of resistance to erlotinib appeared to be activation of the AKT survival pathway such that inhibition with EGFR-TKIs was less effective. Upregulation or alterations in the AKT survival pathway have been previously associated with cisplatin-resistance in other ovarian cell models (Lee et al., 2005b; Yang et al., 2006).

Gefitinib sensitivity has also been examined in A2780 and the cisplatin-resistant subline A2780/Pt (Servidei et al., 2008). The A2780/Pt cells were more sensitive to gefitinib (Table 1). The A2780/Pt cells had no increase in EGFR or pEGFR protein expression; rather they had increased expression and activation of two of EGFRs' binding partners, HER-2 and HER-3. This model shows that sensitivity to gefitinib can occur in

cell models with constitutive activation of HER2 signalling pathways. The A2780/CDDP and A2780/Pt cell models highlight the fact that different mechanisms of platinum resistance can develop independently from the same parental cell line, and this consequently affects the cross-resistance profile to other agents such as EGFR-TKIs.

Benedetti *et al.* investigated the response to gefitinib in two platinum-resistant ovarian cancer cell lines, IGROV-1/Pt1 and IGROV-1/OHP, developed with cisplatin and oxaliplatin, respectively (Benedetti et al., 2008). Both platinum-resistant cell lines exhibited cross-resistance to gefitinib **(Table 1).** The cell lines had reduced expression of EGFR and pEGFR protein. Cross-resistance to gefitinib appeared to be caused by decreased apoptosis in response to treatment with the TKI, again being associated with increased AKT activity.

Figure 1 summarises the molecular changes in platinum-resistant cell lines from Table 1 that contribute to the response to EGFR-TKIs **(Figure 1).** The decision tree diagram divides the cisplatin-resistant cell lines into subgroups based on response to EGFR-TKIs. There are multiple categories, showing a different pattern of molecular markers, for EGFR-TKI sensitivity and resistance highlighting the complexity of using molecular markers in the clinic to predict the outcome of EGFR-TKI therapy. Upregulation of the AKT survival pathway and anti-apoptosis mechanisms of resistance may cause cross resistance to both platinums and EGFR-TKIs but this does not occur frequently enough for cross resistance to be a common phenotype in cell models. Only 3 out of 10 platinum-resistant models found in this systematic review were cross resistant to both platinums and EGFR-TKIs. The same numbers of models, 3 out of the 10, were actually more sensitive to EGFR-TKIs than the parental cell lines that they were derived from. These models had activation of the EGFR or activation of an EGFR binding partner. Therefore, EGFR-TKIs have a promising future in the salvage chemotherapy of platinum-resistant cancers as only 30% of cell lines show a cross-resistance phenotype, the remaining 70% remain sensitive or have become hypersensitive to EGFR-TKIs.

*3.2. Erlotinib in non-small cell lung cancer*

The literature search for clinical trials using erlotinib for the treatment of platinum pretreated NSCLC identified 6 studies, 5 single-agent and 1 combination regimen **(Table 2A)**. In all studies patients had received at least one cycle of prior chemotherapy and patients were assessed for response by either RECIST or WHO response criteria.

There were 5 studies which reported the use of 150 mg/day single-agent erlotinib for the treatment of platinum pretreated NSCLC **(Table 2A**). The pooled overall response rate of all patients including all platinum refractory, resistant, sensitive and unknown status patients was 11.14% (72 responders/646 patients) (Perez-Soler et al., 2004; Shepard et al., 2005; Lilenbaum et al., 2008; Kubota et al., 2008; Felip et al., 2008). In

studies which provided separate data for the platinum-refractory cohort, the overall response rate was similar, being 10% (16 responders/ 160 patients) (Shepard et al., 2005; Felip et al., 2008). This suggests that it is likely that many of the "unknown" or unreported platinum-resistance status patients were most likely platinum refractory or resistant, as one generally observes higher response rates in platinum-sensitive cohorts (Stordal et al., 2007b; Stordal et al., 2007c). The overall response rate was higher in the one study with 100% of patients being of Asian ethnicity 28.3% (17 responders / 60 patients) (Kubota et al., 2008) and this difference is significant ($p = 0.0097$) **(Figure 2).** Several studies investigated EGFR mutations, copy number or EGFR protein expression by immunohistochemistry (IHC), although the number of patients assessed for biomarkers was much smaller than the whole treated numbers, often due to the lack of availability of tumour samples. The two studies which examined EGFR expression by IHC reported similar response rates in EGFR positive patients to the overall response rates, 11.65% (19 responders/163 patients). The response rates in patients with mutations in the EGFR gene or increased gene copy number were much higher, 41.6% (5 responders/12 patients) and 33.33% (5 responders/15 patients), respectively (Kubota et al., 2008; Felip et al., 2008). These differences in response rate were statistically significant, $p = 0.008$ and $p = 0.0224$, respectively **(Figure 2**). This suggests that EGFR mutations and copy number changes are predictive of response to erlotinib in platinum pretreated NSCLC patients.

Survival data were also presented in the single-agent erlotinib studies. The weighted mean PFS and OS for erlotinib in all patients were 2.24 ($n = 544$) and 8.12 ($n = 573$) months respectively (Perez-Soler et al., 2004; Shepard et al., 2005; Lilenbaum et al., 2008; Kubota et al., 2008). One year survival data was only given in two studies; the weighted mean was 45.40%, $n = 86$ (Perez-Soler et al., 2004; Kubota et al., 2008). PFS and OS were also longer in patients in the Felip *et al*. study with EGFR mutations 205 days vs. 43 days and 205 days vs. 113 days, compared to patients with wild-type EGFR although both were non-significant due to low patient numbers (Felip et al., 2008).

Two combination erlotinib studies were identified where erlotinib was combined with bevacizumab or pemetrexed (Herbst et al., 2007; Ranson et al., 2010). The bevacizumab combination resulted in slightly higher response rates, 17.9% (7 responders / 39 patients), and longer PFS and OS, 4.4 and 13.7 months, respectively (Herbst et al., 2007). However, the pemetrexed combination gave similar outcomes to single-agent erlotinib (Table 2A).

*3.3. Gefitinib in Non-small Cell Lung Cancer*

The literature search for clinical trials using gefitinib for the treatment of platinum pre-treated NSCLC identified 16 studies, 12 single-agent and 4 combination regimens

**(Table 2B**). In all studies, patients had received at least one cycle of prior chemotherapy and patients were assessed for response by either RECIST or WHO response criteria.

There were 10 studies which reported the use of 250 mg/day, single-agent gefitinib for the treatment of platinum-pretreated NSCLC **(Table 2B).** The pooled overall response rate of all patients, including all platinum refractory, resistant, sensitive and unknown status patients, was 15.25% (231 responders/1515 patients) (Fukuoka et al., 2003; Kris et al., 2003; Santoro et al., 2004; Kim et al., 2008; Maruyama et al., 2008; Lee et al., 2010; Natale et al., 2009a; Zhang et al., 2005; Chen et al., 2007; Wang et al., 2008). One study exclusively examined platinum-refractory patients and the overall response rate was similar, 18.1% (19 responders/ 103 patients) (Fukuoka et al., 2003). The overall response rate was higher in studies with patients of Asian ethnicity, 29.17% (140 responders / 480 patients) (Kim et al., 2008; Maruyama et al., 2008; Zhang et al., 2005; Chen et al., 2007; Fukuoka et al., 2003; Wang et al., 2008), this difference from the total patient population was statistically significant, p = <0.0001 **(Figure 2).**

Several studies investigated EGFR mutations, copy number as well as EGFR and pEGFR protein expression by IHC, although again with smaller patient numbers. The response rates in patients with mutations in the EGFR gene or increased pEGFR were significantly higher, 63.89% (23 responders/36 patients) and 60.0% (6 responders/10 patients), respectively, $p < 0.0001$ and $p = 0.0016$ (Maruyama et al., 2008; Chen et al., 2007; Wang et al., 2008). This suggests that EGFR mutations and phosphorylation of EGFR are predictive of response to gefitinib in a platinum-pretreated, relapsed NSCLC population. **(Figure 2).** Increased EGFR expression by IHC and increased copy number of the EGFR gene also led to significantly higher response rates of 34.7% (8 responders / 23 patients) and 45.45% (5 responders / 11 patients), respectively, $p = 0.0178$ and $p = 0.0176$. This correlates with our own preclinical findings from the systematic review in Section 3.1; an increased expression of pEGFR is more strongly associated with sensitivity to EGFR-TKIs than an increase in EGFR alone as the pathway is active and therefore sensitive to inhibition **(Figure 1).**

Survival data were also presented in the single-agent 250 mg/day gefitinib studies. The weighted mean PFS, OS and 1 year survival for gefitinib in all patients were 2.82 (n = 1340) and 8.64 (n = 1493) months and 34.49% (n = 1223), respectively (Fukuoka et al., 2003; Kris et al., 2003; Santoro et al., 2004; Kim et al., 2008; Maruyama et al., 2008; Lee et al., 2010; Natale et al., 2009a; Zhang et al., 2005; Chen et al., 2007; Wang et al., 2008). PFS and OS were longer in Asian patients, 4.05 (n = 429) and 12.68 (n = 407) months, respectively (Kim et al., 2008; Maruyama et al., 2008; Zhang et al., 2005; Chen et al., 2007; Wang et al., 2008).

There were two studies which reported the use of 500mg/day single-agent gefitinib for the treatment of platinum-pretreated NSCLC (Table 2B). The pooled overall

response rate of all patients including all platinum refractory, resistant, sensitive and unknown status patients was 13.2% (29 responders/219 patients) (Fukuoka et al., 2003; Kris et al., 2003). The response rate of the platinum refractory patients from the Fukuoka *et al.* study was 18.0%. The increased dose of gefitinib did not improve any clinical outcomes in both studies and was associated with more adverse events. Therefore 250mg/day is proposed as the standard dose of administration.

Four studies were identified that used a combination gefitinib regimen for the treatment of platinum-pretreated NCSLC (Table 2B) (Chen et al., 2007; Gadgeel et al., 2007; O'Byrne et al., 2007; Ramalingham et al., 2008). Response rates vary largely between the studies, as high as 52% when combined with vinorelbine in an Asian population (Chen et al., 2007) and as low as 0% when combined with cetuximab in a non-Asian population (Ramalingham et al., 2008).

*3.4. Erlotinib and Gefitinib in Ovarian Cancer*

No small molecule TKI is currently approved for use in ovarian cancer, but several clinical trials have investigated the use of either erlotinib or gefitinib as second line therapy. The literature search for clinical trials using erlotinib or gefitinib for the treatment of platinum pretreated ovarian cancer identified 6 studies (Table 3). In all studies, patients had received at least one cycle of prior chemotherapy and patients were assessed for response by either RECIST or WHO response criteria.

A single arm, phase II study was conducted by Gordon *et al.* to evaluate erlotinib (150 mg/day) as a treatment option for platinum-resistant or -refractory patients with ovarian cancer (n=34) (Gordon et al., 2005). All tumours were confirmed to be EGFR protein expression positive by IHC. The objective response rate was 6% (partial responses) and median survival was 8 months. Hirte and colleagues investigated the effect of addition of erlotinib (150 mg/day) to salvage carboplatin chemotherapy (AUC 5/21 days) for ovarian cancer patients who had previously received platinum-based drugs (Hirte et al., 2010). Their trial consisted of two arms to distinguish platinum-sensitive and -resistant patients (n=34 and 17, respectively). The ORRs were 57% for platinum-sensitive and 7% for platinum-resistant patients. For platinum-sensitive patients with EGFR positive tumours as determined by IHC, there were 12 responses (60% ORR), and in the platinum-resistant arm, the responding patient was EGFR-positive. The addition of bevacizumab to erlotinib gave a higher response rate in a platinum refractory/resistant population 23.1% (Chambers et al., 2010).

A phase II trial conducted by Posadas *et al.* investigated the phosphorylation status of EGFR following daily treatment with gefitinib (500 mg/day) and observed no objective responses amongst the ovarian tumours of 16 previously-treated patients who they evaluated (Posadas et al., 2007). All patients were EGFR-positive and decreases of

both EGFR and pEGFR were noted in 50% of cases. The publication does not state explicitly that patients have received prior platinum. However, in a heavily pretreated population, many with >5 cycles, we are presuming platinum pretreatment. While all patients were recipients of previous chemotherapy and had progressive disease, no information was provided about the constituent therapeutics of their prior treatment or their time to relapse and, hence, resistance status. In the trial conducted by Schilder *et al*. (Schilder et al., 2005), 27 evaluable patients were treated with gefitinib (500 mg/day), of whom 17 were confirmed to be platinum-resistant. From this subgroup, 1 partial response was observed (5.9%). This patient was the only responder observed in the overall study group, and was confirmed to have EGFR protein expression as well as an EGFR mutation. Four patients, each of whom were platinum-resistant, experienced prolonged PFS (>9 months) above the median PFS (2.2 months). These patients were EGFR protein expression positive; however, these responses did not correlate with intensity of EGFR staining by immunohistochemistry. Four patients in this study had primary peritoneal rather than ovarian cancer and this data cannot be separated.

The addition of gefitinib (500 mg/day) to tamoxifen (40 mg/day) salvage therapy was investigated by Wagner *et al.*; all patients were either refractory or resistant to platinum chemotherapy (n=56). There were no responders to the combination regimen during the trial, while 28·6% of patients had stable disease while on treatment (Wagner et al., 2007). The addition of gefitinib (500 mg/day) to paclitaxel (175mg/m$^2$) and carboplatin (AUC5/21 days) was investigated by Pautier *et al*.; patients were stratified as either resistant (n=21) or sensitive (n=42), response rates were 19.2% and 61.9% and overall survival 16.9 and 25.7 months, respectively (Pautier et al., 2010). These are the best response rates and survival rates identified in the review for EGFR-TKIs for the treatment of platinum-resistant ovarian cancer. However they appear to have more to do with the success of the combination regimen of carboplatin and paclitaxel than the gefitinib. Both of these studies included a small minority of patients with fallopian tube or primary peritoneum cancer and data can not be separated from the ovarian cancer patients.

## 4. Discussion

A primary goal of anticancer therapy is to stop tumour cells from proliferating and to induce selective tumour cell death. This goal may be achieved by disruption of signalling pathways essential for growth, division, differentiation and/or invasion of tumour cells, causing arrest of the cell cycle or by sensitising the cells to apoptosis/anoikis, (Giménez-Bonafé et al., 2009; Westhoff and Fulda, 2009). EGFR is an important cell surface receptor mediating downstream survival signalling and has become an important target for new cancer therapeutics. This has led to the approval of erlotinib and gefitinib in NSCLC because of tremendous benefit to an identifiable subpopulation of patients, specifically those with EGFR mutations (Gadgeel et al., 2010) which result in

dependence of the tumour cells on the mitogenic downstream signalling *via* EGFR, a phenomenon referred to as "oncogene addiction" (Weinstein and Joe, 2008). Erlotinib and gefitinib also have a relatively minimal toxicity profile when compared to other chemotherapeutics such as carboplatin and taxol; a rash is the most common side effect of the EGFR-TKIs, whereas the standard chemotherapy agents cause a wide range of adverse events (Lilenbaum et al., 2008; Mok et al., 2009).

### *4.1. Preclinical efficacy of EGFR-TKIs in platinum-resistant cell lines and implications for clinical treatment.*

The diversity of possible responses to erlotinib and gefitinib in platinum-resistant cell lines is evident in Table 1. With relatively few studies found by literature search we have described platinum-resistant cell lines which are sensitive, resistant or show no change in response to EGFR-TKIs. This poses a challenge for the clinical treatment of platinum resistant cancer, how to identify which patients may benefit from second line therapy with erlotinib or gefitinib? Figure 1 is a summary of the mechanisms of resistance or sensitivity to EGFR-TKIs identified in this systematic review. We have identified two separate mechanisms of EGFR-TKI sensitivity; activation of the EFGR pathway or activation of an EGFR binding partner and consequent pathway (HER-2, HER-3). We have also identified two separate mechanisms of resistance, a defect in apoptosis or AKT signalling in response to treatment with an EGFR-TKI **(Figure 1).**

As we have seen from the clinical studies identified in this systematic review, some have examined EGFR mutation (Kubota et al., 2008; Felip et al., 2008; Maruyama et al., 2008; Chen et al., 2007), copy number (Kubota et al., 2008; Chen et al., 2007) and some protein expression of EGFR (Perez-Soler et al., 2004; Shepard et al., 2005; Maruyama et al., 2008) or pEGFR (Chen et al., 2007). Figure 1 demonstrates how the expression and activity of many other proteins and pathways apart from EGFR will influence the overall outcome of EGFR-TKI treatment. Indeed, as is evident from our decision tree diagram, the analysis of EGFR expression alone will not segregate the resistant from the sensitive models. Even when EGFR expression is increased, pEGFR expression needs to be evaluated to determine if EGFR-TKI sensitivity can occur, and sensitivity can occur by other mechanisms such as *via* other ErbB family members and their downstream signalling molecules, at a minimum. If clinical studies are going to be able to use biomarkers to stratify patients for therapy they would need to examine the protein expression of EGFR, pEGFR, HER-2, HER-3, pHER-2, pHER-3, AKT, pAKT and markers of apoptosis to be able to categorise a patient as potentially EGFR-TKI responsive.

Gadgeel and collegues have recently published a decision tree diagram for the treatment options for NSCLC. Their algorithm uses EGFR mutation, EML4/ALK+, ERCC1/RRM1 low, ERCC1/TS low and ERCC1 high to choose between treatment with erlotinib or gefitinib, crizontib, platinum/gemcitabine, platinum/premetrexed or taxane/non-platinum (Gadgeel et al., 2010). Our decision tree diagram adds to this by showing in preclinical models that if enough members of the EGFR family and other proteins are assayed it is possible to categorise cell lines as sensitive to EGFR-TKIs even where EGFR is not mutated and in a platinum-resistance setting. A review has recently been published about the predictive value of KRAS mutations in NSCLC and predicting the outcome of EGFR targeted therapy (Roberts et al., 2010). Mutations in KRAS, EML4-ALK translocations and EGFR are mutually exclusive in NSCLC patients (Roberts et al., 2010). An association between a mutation in KRAS and a lack of response to EGFR-TKIs has been observed, but it is unclear of the impact on survival (Roberts et al., 2010). By examining KRAS mutation status, EGFR mutation status can be confidently predicted. However, the EGFR pathway could still be activated at the protein level and EGFR-TKIs may be of benefit in a subset of patients.

*4.2. The EGFR-TKI resistant phenotype*

Work by Galetti and colleagues indicates that resistance to gefitinib does not appear to be related to the uptake of the drug, as the rate of uptake was comparable between both intrinsically gefitinib-sensitive and -resistant NSCLC cell lines (Galetti et al., 2010). Janmaat and colleagues demonstrated that cell death following EGFR inhibition resulted from apoptosis mediated by the inactivation of both MAPK kinase and PI3K in NSCLC cell lines. Hence, activation mutants downstream in either of these pathways may cause resistance to EGFR-TKIs (Janmaat et al., 2003). Support for this is provided by studies in which AKT activity was de-coupled from upstream PI3K; treatment with gefitinib did not effect cell death when AKT was activated *via* tensin homolog (PTEN) down-regulation (Bianco et al., 2003; She et al., 2003; Yamamoto et al., 2010). Furthermore, Morgillo and colleagues showed that levels of pAKT were increased in Calu-3 cell lines with acquired resistance to either erlotinib or gefitinib (Morgillo et al., 2010). Cisplatin resistance has been frequently associated with an activation of the PI3K and AKT pathway in ovarian cancer (Lee et al., 2005b; Yang et al., 2006) and NSCLC cancer cells (Chin et al., 2008). This is therefore a potential mechanism of cross-resistance between the two classes of agents.

The cellular signals transduced by EGFR are mediated by several other kinases whose activity is usually dependent on activation by pEGFR. Any of these enzymes may themselves become mutated and this can lead to a constitutively active pathway. This constitutively active pathway will remain active regardless of EGFR blockade, hence, furnishing an EGFR-TKI-resistant phenotype. This situation has been similarly described for KRAS (Schubbert et al., 2007), which is estimated to be mutated in 14% of ovarian

cancers, amalgamating all histological subtypes, based on data collected in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (Bamford et al., 2004) and 16% of NSCLC, as described recently by Mao *et al*. (Mao et al., 2010). It is worth considering whether administration of platinum-based chemotherapeutics may itself select for such mutants and in effect induce these EGFR-bypassed mutants.

*4.3. Erlotinib and gefitinib as salvage therapy for platinum-resistant NSCLC*

The overall response rate in platinum pretreated NSCLC to erlotinib (150 mg/day) and gefitinib (250 mg/day) were 11.14% and 15.25%, respectively. Gefitinib had a significantly higher response rate ($p = 0.0122$) **(Figure 2).** This highlights the power of pooling data across multiple studies to yield higher patient numbers, n = 646 for erlotinib and n = 1515 for gefitinib. Gefitinib should therefore be the EGFR-TKI of choice in platinum-pretreated NSCLC. Interestingly, gefitinib is also superior to erlotinib in patients with an overexpression of EGFR measured by IHC, 34.7% vs 11.65%, p=0.0077. This suggests that there may be a benefit of gefitinib in patients with overexpression/activation of the EGFR pathway. Gefitinib also outperforms erlotinib in patients with EGFR mutations but this difference was not significant. The results of the pooled analysis of this review suggest that being EGFR-mutation positive, increased copy number positive or having increased protein expression of EGFR/pEGFR leads to significantly improved response rates to EGFR-TKIs used as salvage chemotherapy in platinum pre-treated NSCLC **(Figure 2).** This expands the cohort of NSCLC patients which may benefit from EGFR-TKIs after failure of platinum chemotherapy. However, patients with activating EGFR mutations or increased pEGFR expression are still relatively rare in the NSCLC population before and after platinum chemotherapy so other agents need to be investigated in this patient cohort.

EGFR-TKIs perform better in platinum pretreated NSCLC when compared to placebo and docetaxel. Shepherd and colleagues compared erlotinib (150 mg/day) with placebo; erlotinib had an 8.9% response rate (38 responders / 427 patients) compared with 0.94% for placebo (2 responders / 211 patients) (Shepherd et al., 2005). The INTEREST trial compared gefitinib (250 mg/day) with docetaxel (75 mg/m$^2$). The overall response rates were 9.1% for gefitinib (66 responders / 723 patients) and 7.6% for docetaxel (54 responders /710 patients) ($p > 0.05$). A modest improvement in overall survival was also noted, 8.0 *vs* 7.6 months in favour of gefitinib. The study also demonstrated lesser toxicity resulting from gefitinib treatment, with incidence of adverse events occurring in 4% of patients versus 18% of those given docetaxel (Kim et al. 2008). A more dramatic difference was shown in the ISTANA trial in an Asian patient population comparing the same doses of gefitinib and docetaxel as the INTEREST trial. The overall response rate for gefitinib treatment was 28.1% (23 responders / 83 patients) *vs* 7.6% for docetaxel ($p < 0.001$). Median survival was also 2 months longer with gefitinib, but this was not significant (Lee et al., 2010).

*4.4. Erlotinib and gefitinib as salvage therapy for platinum-resistant ovarian cancer*

Studies have demonstrated a correlation between high expression levels of EGFR in patients with ovarian carcinoma and poor prognosis for both disease-free and overall survival (17 vs 31 months; p = 0.0001 and 12 vs 22 months; p = 0.0005, respectively) (Psyrri et al., 2005). Expression of EGFR was assessed by immunohistochemistry in ovarian tumours from patients who had gone on to receive standard platinum/paclitaxel combination therapy. It has been demonstrated, using tissue lysate arrays, that administration of gefitinib to ovarian cancer patients does indeed decrease the phosphorylation of EGFR and its' associated downstream signalling molecules, including AKT (Posadas et al., 2007). This work also demonstrates the feasibility of observing target-specific effects of TKI activity *in vivo*. Notably, reduction in phosphorylation did not translate into objective responses in this heavily pretreated patient cohort.

The response rate to single agent erlotinib or gefitinib in platinum-pretreated ovarian cancer was overall very low 0-5.9%, this rate was slightly higher in patients who had been characterised as EGFR-positive 5.9-9%. However, these response rates are much lower than that of single-agent oxaliplatin or paclitaxel in platinum-resistant cancers, 8% and 22%, respectively (Stordal et al 2007b, Stordal et al. 2007c). These two previous systematic reviews could more strictly examine the platinum-resistant and the platinum-sensitive patients separately. Hence, we are seeing higher response rates to oxaliplatin and paclitaxel in a cohort of patients that we would expect to respond poorly to continued chemotherapy. If we had been able to discriminate between resistant and sensitive patients for the erlotinib and gefitinib studies, chances are the response rates would be even lower.

The response rates of combination erlotinib or gefitinib therapy in ovarian cancer are considerably higher, 7.1-19.2% in the platinum refractory/resistant cohorts and 56.7-61.9% in the platinum-sensitive cohorts **(Table 3)**. Unfortunately, none of these studies performed a direct comparison between chemotherapy and the addition of the EGFR-TKI to the combination regimen. However, from our previous review on paclitaxel for the treatment of platinum-resistant cancers, we can see that the response rates for the addition of erlotinib or gefitinib are not any higher than the response rates of platinum/taxane combination chemotherapy in both platinum-resistant (32%) and platinum-sensitive disease (79.5%) (Stordal et al., 2007c).

*4.5. Availability of tissue for molecular marker analysis*

In two of the largest studies of single-agent gefitinib in platinum pre-treated NSCLC, IDEAL-1 and IDEAL-2 (Fukuoka et al., 2003; Kris et al., 2003), molecular profiling of EGFR mutations was published in a separate publication after the initial clinical trial publications (Bell et al., 2005). IDEAL-1 and IDEAL-2 had a combined

patient enrolment of 424; only 119 patient tumour samples were available for molecular analysis (28%). Of these, an even smaller number were usable for EGFR sequencing (n = 79) and copy number analysis (n = 90). 13 EGFR mutations were detected, and 6 of these patients responded to gefitinib therapy (Bell et al., 2005). Unfortunately, the way the data is reported in the Bell *et al.* study, it can't be determined if these patients came from IDEAL-1 or IDEAL-2 or any other clinical parameters for the responders. This highlights the importance of designing clinical trials with a molecular profiling focus to have tissue collection as mandatory for patient enrolment (Fojo and Parkinson, 2010).

*4.6. Other TKI therapeutic strategies for platinum-resistant cancers*

In practice, therapy with EGFR-TKIs does not yield a complete durable response. Alternating treatment between erlotinib and gefitinib may not prove adequate, as cross-resistance studies on NSCLC-derived Calu-3 cell lines have shown (Morgillo et al., 2010). The erlotinib-resistant cell line was resistant to gefitinib and *vice versa* due to similar mechanisms of resistance. TKIs, directed against EGFR, which also have specificity for other signalling kinases are likely to be less prone to mutation-derived inactivity as they can target alternate pathways. For example, the dual specificity of lapatinib for EGFR and ErbB2 indicates that it should exhibit a potent inhibition of EGFR/ErbB2 heterodimers. Therefore, even without direct binding to EGFR, lapatinib may inhibit some of the cellular effects mediated by ErbB2, such as cell proliferation (Hsieh et al., 2000).

Many other TKIs, currently undergoing clinical trials for the disruption of tumour angiogenesis and specific for a VEGFR have been examined as therapies for platinum-resistant ovarian cancer or NSCLC; cediranib (Hirte et al., 2008; Matulonis et al., 2009); pazopanib (Friedlander et al., 2010); sorafenib (NCT01047891; Blumenschein, Jr. et al., 2009); sunitinib (Biagi et al., 2010; Ping et al., 2010; Novello et al., 2009; Socinski et al., 2008); vandetanib (Annunziata et al., 2010; Natale et al., 2009a). This strategy so far appears to have had limited success in chemo-resistant NSCLC or ovarian cancer. This is even the case for TKIs which have multiple specificities. For example, vandetanib, the small molecule inhibitor of both VEGFR-2 and EGFR, would be expected to prove particularly versatile as it can contribute to the amelioration of angiogenesis via VEGFR-2 inhibition and prevent the EGFR-induced production of angiogenic growth factors and activation of tumour adjacent endothelial cells, in addition to the putative effects on the cell cycle progression of EGFR inhibition. However, clinical studies have so far shown vandetanib to offer only modest extensions to progression-free survival of patients with late-stage NSCLC (over erlotinib/gefitinib) either alone or in combination with other agents. The phase III 'Zactima Efficacy when Studied versus Tarceva' (ZEST) trial illustrates this in a direct comparison between vandetanib and erlotinib monotherapies for previously treated NSCLC; both arms display an overall response rate of 12% (Natale et al., 2009b). These TKIs may be of greater benefit if administered in ovarian cancer and

NSCLC at earlier stages during tumour development, where angiogenesis is still predominantly reliant on VEGFR activity (Morabito et al., 2009) and hence more likely to prove susceptible to VEGFR inhibition. However, in practical terms, such early detection is difficult to achieve and relies on the discovery of novel, early biomarkers.

**5. Future Developments and conclusions**

The detection of mutated or up-regulated targets for EGFR-TKIs may allow for a personalised treatment for NSCLC but also potentially other cancer types. Any such molecular targets which are seen to be prevalent in many patients in a cohort may serve as reliable biomarkers or become the focus of efforts to develop further inhibitors as new chemotherapy agents. Such is the success of treatment of NSCLC tumours with an acquired translocation of EML4 with ALK leading to the expression of an oncoprotein termed EML4-ALK. Crizotinib, an ALK inhibitor has shown dramatic clinical benefit to this cohort of NSCLC (Gerber et al., 2010). Genomic profiling techniques can enable prediction of patient response to treatment and prognostication of treatment outcome (Fehrmann et al., 2007). Promising proof-of-concept for this emerging facet of patient care has been developed by Dressman and colleagues for advanced ovarian cancer, wherein a genetic screening/signalling pathway-analysis protocol is employed for prediction of patients' platinum-resistance status at diagnosis of disease and has been shown to do so with a precision of 84% (Dressman et al., 2007).

There are substantial technical difficulties impeding progress in this regard –time and cost primary among them– but nonetheless the number of studies employing 'biomic' technologies to cancer cell lines or tissue samples has seen a marked increase over the last decade (Jacob et al., 2009). The response of individual patients to chemotherapeutics which are administered without biomic profiling of the tumour is likely suboptimal as a result of lack of expression of the drugs' cognate target, evolution of compensatory mechanisms for cell survival or overexpression of drug disposal machinery. Thus, a focus on the development of robust and cost-effective diagnostic technologies for the detection of these biomarkers or responsive phenotypes (Roukos, 2010) will enable tailored treatment to be issued to the patient and have profound benefit. Our understanding of the signalling network under control of EGFR in tumour cells has increased enormously, further aided by advanced functional proteomics technologies (Kolch and Pitt., 2010). The insights offered by this 'surveillance' of the "cell-at-work" should enable a dissection of the reasons underlying the failure of present generation anti-cancer drugs where it occurs.

The overall indication given by the preclinical and clinical evidence is that administration of neither erlotinib nor gefitinib alone is capable of effecting a profound extension in overall survival for patients with platinum pre-treated ovarian cancer or NSCLC. However, EGFR-TKIs appear to be a good current choice for the treatment of

relapsed NSCLC when compared to other salvage chemotherapy such as docetaxel. Response rates are higher still in patients of Asian ethnicity and/or patients with EGFR activating mutations or EGFR pathway activation. EGFR-TKIs do not appear to be suitable for the treatment of platinum pre-treated ovarian cancer than standard chemotherapy agents such as paclitaxel.

Ultimately, determination of a molecular profile of each patient's tumour should enable better treatment and extend survival for a greater number of patients, including those who had previously failed platinum chemotherapy. The major downfall of many of the studies we have reported on is the lack of availability of tumour biopsy material. Tissue collection needs to be mandatory in this age of molecular profiling and the desire to move towards personalised chemotherapy.

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## Figure Legends

**Figure 1** – Decision tree diagram for dividing cisplatin resistant cell lines into subgroups based on response to treatment to EGFR-TKIs. Models described in this diagram are characterised in Table 1.

**Figure 2** – Overall response rates to single-agent erlotinib and gefitinib in NSCLC patient subgroups. Open bars represent erlotinib (150 mg/day) and closed bars represent gefitinib (250 mg/day). Numbers above each bar are the total patient number in each subgroup. Studies used to prepare this diagram are summarised in Tables 2A and 2B. * Indicates a significant difference in the response rate of the subgroup compared to the total patient population. # Indicates a significant difference between the response rates to treatment with erlotinib or gefitinib. Fisher's exact test was used, with significance $p<0{\cdot}05$.

**Table 1.** Platinum-resistant cell lines reporting resistance to erlotinib or gefitinib.

| Parent Cell Line | Cancer Type | EGFR Mutation | Resistant Cell Line | Developed With | Fold Resistance | | | EGFR in Resistant Cell Line | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Platinum (Selecting Agent) | Erlotinib | Gefitinib | EGFR Mutation | EGFR Protein | pEGFR Protein | |
| A2780 | Ovarian | No Servidei *et al*., 2008 | A2780/CDDP | Cisplatin | 14.9 | 0.93 | - | ND | ↓ | ND | Dai *et al.*, 2005 |
| ME180 | Cervical | No Aris-Pulido et al 2008 | AE-ME180/CDDP | Cisplatin | 9.3 | <0.05 | - | ND | ↑ | ↑ | |
| HT212/9 | Cervical | ND | HT212/11/CDDP | Cisplatin | 4.5 | <0.86 | - | ND | ↑ | X | |
| HT180/8 | Cervical | ND | HT180/1/CDDP | Cisplatin | 9.6 | 1.0 | - | ND | ↑ | X | |
| LoVo | Colon | No Nagahara et al 2005 | LoVo/CDDP | Cisplatin | >1.6 | 1.0 | - | ND | ↓ | ND | |
| PC9 | NSCLC | Yes | PC9 (CR) | Cisplatin | >6 | ~2-5 | - | Yes,. | ↓ | ↑ | Chin *et al*., 2008 |
| A2780 | Ovarian | No | A2780/Pt | Cisplatin | 10 | - | 0.60 | No | X | X | Servidei *et al*., 2008, 2001 and 2006 |
| U87-MG | Glioma | No | U87-MG/Pt | Cisplatin | 4.8-16 | - | 0.57 | No | X | X | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| IGROV-1 | Ovarian | No | IGROV-1/Pt1 | Cisplatin | 14 | - | 51 | No | ↑ | X | Benedetti *et al.*, 2008 |
| IGROV-1 | Ovarian | No | IGROV-1/OHP | Oxaliplatin | 73 | - | 19 | No | ↑ | X | |

ND – Not Determined, X – No Change.

**Table 2A.** Clinical trials reporting the administration of erlotinib to patients with platinum pre-treated, relapsed NSCLC.

| Study | Regimen mg/day | Asian Population | Evaluable Patients TKI Treatment Arm | Platinum Status | | | | Response | | | | | | EGFR Detection Method | Survival | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Refractory | Resistant | Sensitive | Unknown | Progressive Disease | Stable Disease | Partial Response | Complete Response | Overall Response Rate % | EGFR + Responders | | Progression Free Survival (months) | Median Overall Survival (months) | 1 year Survival |
| **Erlotinib Single Agent** | | | | | | | | | | | | | | | | | |
| Perez-Soler et al 2004 | 150 | 1.8 % | 57 | - | - | - | 57 | 28 | 22 | 5 | 2 | 7/57 12.3% | 7/57 12.3% | Protein IHC | 2.25 | 8.4 | 40% |
| Shepard et al 2005 | 150 | 12.9% | 427 | 87 | - | - | 340 | 162 | 154 | 35 | 3 | 38/427 8.8% | 12/106 11.3% | Protein IHC | 2.2 | 6.7 | ND |
| Lilenbaum et al 2008 | 150 | ND | 29 | - | - | - | 29 | 14 | 5 | 2 | 1 | 3/29 10.3% | UE | UE | ND | 14.9 | ND |
| Kubota et al 2008 | 150 | 100% | 60 | - | - | - | 60 | 27 | 13 | 17 | 0 | 17/60 28.3% | 3/7 42% | Mutation Exon 19 | 2.56 | 14.7 | 56% |
| Felip et al 2008 | 150 | ND | 73 | 73 | - | - | - | 38 | 28 | 7 | 0 | 7/73 9.5% | 5/15 33%; 2/5 40% | Copy Number FISH; Gene Mutation | UE | UE | ND |
| **Erlotinib Combination** | | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Herbst et al 2007 | 150 + B | 7.7% | 39 | - | - | - | 39 | 19 | 13 | 6 | 1 | 7/39 17.9% | 1/1 100% | EGFR Mutation | 4.4 | 13.7 | 57.4% |
| Ranson et al 2010 | 100-150 + P | ND | 18 | - | - | - | 18 | 7 | 9 | 2 | 0 | 2/18 11.1% | 0/1 0%<br><br>1/12 8.3% | EGFR Mutation<br><br>Protein IHC | ND | ND | ND |

ND – Not Determined in study, UE – Data unable to be extracted from published study, B = Bevacizumab 15mg/kg/ 21days, P = Pemetrexed 500-700 mg/$m^2$/21days.

**Table 2B.** Clinical trials reporting the administration of gefitinib to patients with platinum pre-treated, relapsed NSCLC.

| Study | Regimen mg/day | Asian Population | Evaluable Patients TKI Treatment Arm | Platinum Status | | | | Responders | | | | | | | Survival | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Refractory | Resistant | Sensitive | Unknown | Progressive Disease | Stable Disease | Partial Response | Complete Response | Overall Response Rate % | EGFR + Responders | EGFR Detection Method | Progression Free Survival (months) | Median Overall Survival (months) | 1 year Survival |
| **Gefitinib Single Agent** | | | | | | | | | | | | | | | | | |
| Fukuoka et al 2003 (IDEAL1) | 250 | 49.5% | 103 | 103 | | - | - | 42 | 37 | 19 | 0 | 19/103 18.4% | ND | ND | 2.7 | 7.6 | ND |
| | 500 | 48.5% | 105 | 105 | | - | - | 44 | 34 | 19 | 1 | 19/105 18.0% | ND | ND | 2.8 | 8.0 | ND |
| Kris et al 2003 (IDEAL2) | 250 | ND USA | 102 | - | - | - | 102 | UE | UE | 12 | 0 | 12/102 11.7% | ND | ND | ND | 7 | 27% |
| | 500 | ND USA | 114 | - | - | - | 114 | UE | UE | 9 | 0 | 10/114 8.7% | ND | ND | ND | 6 | 24% |
| Santoro et al 2004 | 250 | ND Italy | 73 | 16 | - | - | 57 | 34 | 32 | 6 | 1 | 7/73 9.5% | 3/9 33.3% | Protein IHC | ND | 4 | 13.1% |
| Kim et al 2008 (INTEREST) | 250 | 21% | 723 | 394 | - | - | 329 | UE | UE | 66 | | 66/723 9.1% | UE | IHC Copy number | 2.2 | 7.6 | 32% |
| Maruyama et al 2008 | 250 | 100% | 245 | - | - | - | 245 | UE | UE | 45 | | 45/200 22.5% | 6/9 67% 5/11 | EGFR Mutation EGFR | 2.0 | 11.5 | 47.8% |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (V-15-32) | | | | | | | | | | | | 46%<br>5/14<br>35.7% | FISH<br>EGFR<br>IHC | | | |
| Lee et al 2010 (INSTANA) | 250 | 100% | 82 | - | - | - | 82 | UE | UE | 23 | | 23/82<br>28.1% | ND | ND | 3.3 | 14.1 | ND |
| Natale et al 2009a | 250 | ND | 85 | - | - | - | 85 | UE | UE | 1 | | 1/85<br>1.1% | ND | ND | 2.02 | 7.4 | ND |
| Chen et al 2007 | 250 | 100% | 27 | - | - | - | 27 | 6 | 6 | 15 | 0 | 15/27<br>55% | UE | ND | 7.1 | 13.3 | 21.2% |
| Fujimoto et al 2010 | Not Stated | 100% | 6 | - | - | - | 6 | - | 2 | 4 | 0 | 4/6<br>67% | 1/6<br>16% | Mutation<br>Exon 19 | UE | UE | ND |
| Bai et al 2009 | Not Stated | 100% | 102 | - | - | - | 102 | - | - | 37 | - | 37/102<br>36% | 22/37<br>59% | Mutation<br>Exons<br>19,21 | 8.6 | 15.9 | ND |
| Zhang et al 2005 | 250 | 100% | 98 | - | - | - | 98 | 32 | 35 | 30 | 1 | 31/98<br>31.6% | 8/12<br>66%<br>6/10<br>60% | Mutation<br>EGFR<br>pEGFR<br>IHC | 7.0 | 12.0 | 53.1% |
| Wang et al 2008 | 250 | 100% | 22 | - | - | - | 22 | 5 | 7 | 7 | 5 | 12/22<br>54.5% | 9/15<br>60% | Mutation<br>Exons<br>18-21 | 8.61 | ND | ND |
| **Gefitinib Combination** | | | | | | | | | | | | | | | | | |
| Chen et al 2007 | 250<br>+ V | 100% | 21 | - | - | - | 21 | 3 | 7 | 11 | 0 | 11/21<br>52% | UE | ND | 12.8 | 23.4 | 57.1% |
| Gadgeel et al | 250 | 8% | 27 | 27 | - | - | - | 19 | 6 | 2 | 0 | 2/27 | ND | ND | 2.2 | 4.6 | 16% |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2007 | + Cel | | | | | | | | | | | 7.4% | | | | | |
| O'Byrne et al 2007 | 250 + R | ND | 42 | - | - | - | 42 | 27 | 13 | 1 | 1 | 2/42 4.7% | ND | ND | 1.83 | 4.8 | ND |
| Ramalingham et al 2008 | 250 + Cet | 0% | 13 | 13 | - | - | - | 8 | 4 | 0 | 0 | 0/13 0% | 0/0 0% | Mutation and Copy Number | ND | ND | ND |

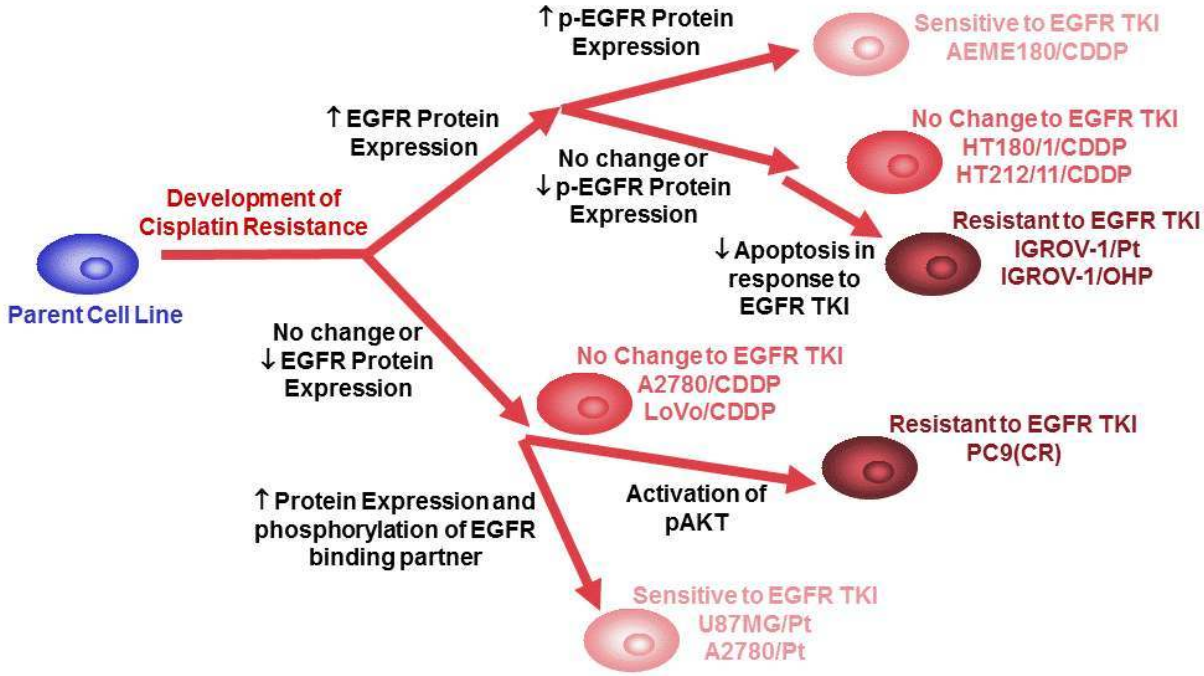
ND – Not Determined in study, UE – Data unable to be extracted from published study, V = Vinorelbine 15mg/$m^2$ 14/days, Cel = Celeoxib 400mg/ twice daily, R = Rofecoxib up to 50mg/day, C = Cetuximab 100-250mg/$m^2$/ 7days.

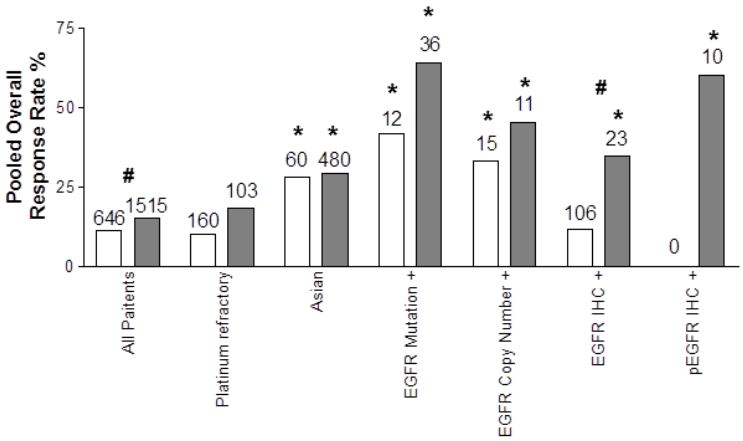
**Table 3.** Clinical trials reporting the administration of erlotinib or gefitinib to patients with platinum pre-treated, relapsed ovarian cancer.

| Study | Regimen | Evaluable Patients TKI Treatment Arm | Platinum Status | | | | Response | | | | | | Survival | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Refractory | Resistant | Sensitive | Unknown | Progressive Disease | Stable Disease | Partial Response | Complete Response | Overall Response Rate % | EGFR Protein Positive Responders | Progression Free Survival (months) | Median Overall Survival (months) | 1 year Survival |
| **Erlotinib Single Agent** | | | | | | | | | | | | | | | |
| Gordon et al 2005 | 150mg/day | 34 | - | - | - | 34 | 17 | 15 | 2 | 0 | 2/34 5.9% | 2/34 5.9% | 2.25 | 8 | 35% |
| **Erlotinib Combination** | | | | | | | | | | | | | | | |
| Hirte et al 2010 | 150mg/day+ Carboplatin 25 AUC/21 days | 49 | - | 17 | - | - | 3 | 10 | 1 | 0 | 1/14 7.1% | 1/13 7.6% | UE | ND | ND |
| | | | - | - | 32 | - | 0 | 13 | 14 | 3 | 17/30 56.7% | 12/20 60% | UE | ND | ND |
| Chambers et al 2010 | 150mg/day + Bevacizumab 10mg/kg | 39 | 39 | | - | - | 20 | 10 | 8 | 1 | 9/39 23.1% | ND | 4.0 | ND | ND |
| **Gefitinib Single Agent** | | | | | | | | | | | | | | | |
| Posadas et | 500mg/day | 16 | - | - | - | 16 | UE | UE | 0 | 0 | 0/16 0% | 0/16 | ND | ND | ND |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| al 2007 | | | | | | | | | | | | 0% | | | |
| Schilder et al 2005 | 500mg/day | 27 | - | 17 | 10 | - | 15 | 8 | 1 | 0 | 1/27 3.7% | 1/11 9% | 2.17 | 12.16 | ND |
| **Gefitinib Combination** | | | | | | | | | | | | | | | |
| Wagner et al 2007 | 500 mg/day + Tamoxifen 40 mg/day | 56 | 56 | | - | - | 40 | 16 | 0 | 0 | 0/56 0% | ND | 1.93 | 8.43 | ND |
| Pautier et al 2010 | 500 mg/day + Paclitaxel 175 mg/m$^2$ and Carboplatin AUC 5/21days. | 68 | 26 | | - | - | 4 | 13 | 4 | 1 | 5/26 19.2% | ND | 6.1 | 16.9 | ND |
| | | | | | 42 | - | 4 | 8 | 16 | 10 | 26/42 61.9% | ND | 9.2 | 25.7 | ND |

ND – Not Determined in study, UE – Data unable to be extracted from published study.


↑ p-EGFR Protein Expression
Sensitive to EGFR TKI
AEME180/CDDP
↑ EGFR Protein Expression
No Change to EGFR TKI
HT180/1/CDDP
HT212/11/CDDP
No change or ↓ p-EGFR Protein Expression
Development of Cisplatin Resistance
Resistant to EGFR TKI
IGROV-1/Pt
IGROV-1/OHP
↓ Apoptosis in response to EGFR TKI
Parent Cell Line
No change or ↓ EGFR Protein Expression
No Change to EGFR TKI
A2780/CDDP
LoVo/CDDP
Resistant to EGFR TKI
PC9(CR)
Activation of pAKT
↑ Protein Expression and phosphorylation of EGFR binding partner
Sensitive to EGFR TKI
U87MG/Pt
A2780/Pt


Pooled Overall Response Rate %
75
50
25
0
646
#
1515
160
103
*
60
*
480
*
12
*
36
*
15
*
11
106
#
*
23
0
*
10
All Paitents
Platinum refractory
Asian
EGFR Mutation +
EGFR Copy Number +
EGFR IHC +
pEGFR IHC +